



A COMPREHENSIVE REVIEW ON – COVID - 19: VACCINATION

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Abstract:

The COVID-19 is a highly transmittable and pathogenic viral infection caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), which is emerged in, China and spread over globe. Genomic analysis revealed that SARS-CoV-2 is phylogenetically related to severe acute respiratory syndrome-like (SARS-like) bat viruses; therefore bats could be the possible primary reservoir. The intermediate source of origin and transfer to humans is not known, however, the rapid human to human transfer has been confirmed widely. There is no clinically approved antiviral treatment available to be used against COVID-19. However, few broad-spectrum antiviral drugs have been evaluated against COVID-19 in clinical trials, resulted in clinical recovery. This review, summarize and analyze the emergence and pathogenicity of COVID-19 infection and previous human corona viruses (SARS-CoV) and (MERS-CoV). We also discuss the post COVID complications, co morbidity and COVID-19 and approaches for developing effective vaccines and therapeutic combinations to cope with this viral outbreak. [

Keywords. COVID 19, SARS, ARDS , CoVZXC21

Introduction:

Corona viruses belong to the Coronaviridae family in the Nidovirales order. Corona represents crown-like spikes on the outer surface of the virus; thus, it was named as a coronavirus. Corona viruses are minute in size (65–125 nm in diameter) and contain a single-stranded RNA as a nucleic material, size ranging from 26 to 32kbs in length (Fig. 1). The subgroups of coronaviruses family are alpha (a), beta (b), gamma (c) and delta (d) coronavirus. The severe acute respiratory syndrome corona virus (SARS-CoV), H5N1 influenza A, H1N1 2009 and Middle East respiratory syndrome corona virus (MERS-CoV) cause acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) which leads to pulmonary failure and result in fatality. These viruses were thought to infect only animals until the world witnessed a severe acute respiratory syndrome (SARS) outbreak caused by SARS-CoV, 2002 in Guangdong, China. Only a decade later, another pathogenic coronavirus, known as Middle East respiratory syndrome coronavirus (MERS-CoV) caused an endemic in Middle Eastern countries.

Recently at the end of 2019, Wuhan an emerging business hub of China experienced an outbreak of a novel coronavirus that killed more than eighteen hundred and infected over seventy thousand individuals within the first fifty days of the epidemic. This virus was reported to be a member of the b group of coronaviruses. The novel virus was named as Wuhan coronavirus or 2019 novel coronavirus (2019-nCov) by the Chinese researchers. The International Committee on Taxonomy of Viruses (ICTV) named the virus as SARS-CoV-2 and the disease as COVID-19. In the history, SRAS-CoV (2003) infected 8098 individuals with mortality rate of 9%, across 26 countries in the world, on the other hand, novel corona virus (2022) infected 53 millions individuals with mortality rate of 2.9%, across all over world ,& about 63 Lakh death till date of this writing. It shows that the transmission rate of SARS-CoV-2 is higher than SRAS-CoV and the reason could be genetic recombination event at S protein in the RBD region of SARS-CoV-2 may have enhanced its transmission ability. In this review article, we discuss the origination of human coronaviruses briefly. We further discuss the associated infectiousness and biological features of SARS and MERS with a special focus on COVID-19.

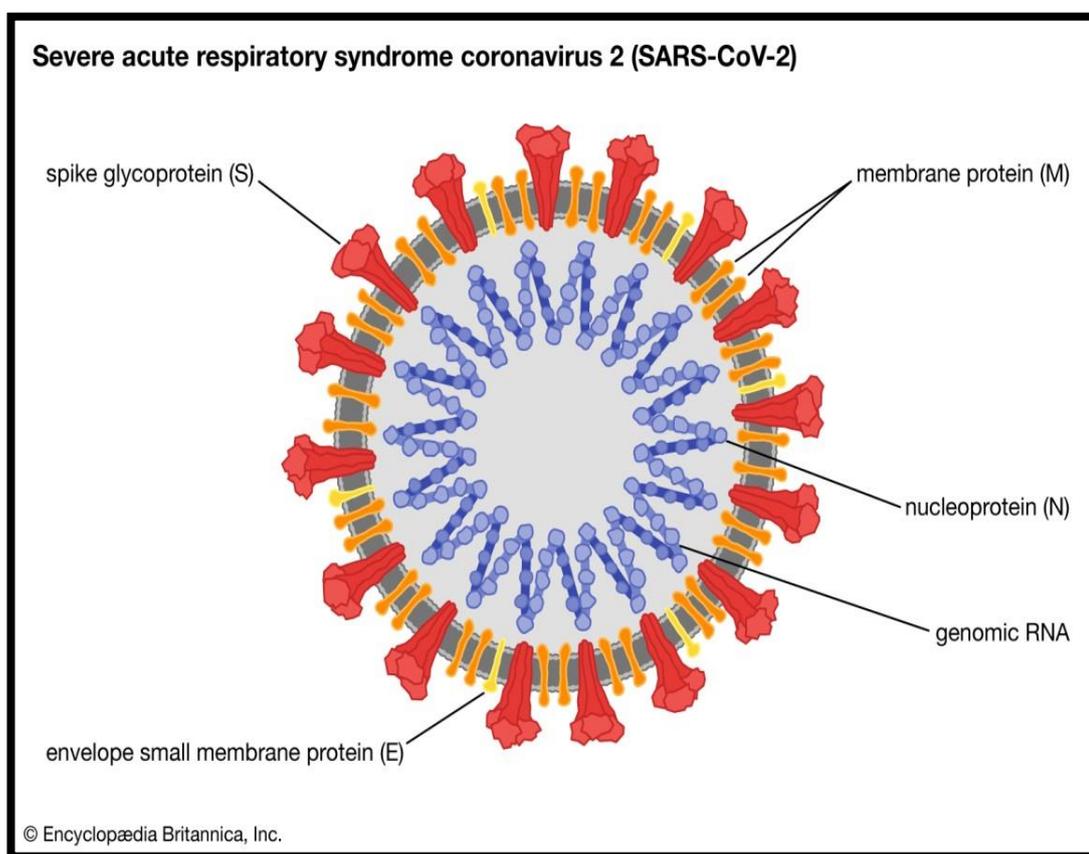


Fig. 1. Structure of respiratory syndrome causing human coronavirus

Comparative analysis of emergence and spreading of coronavirus:

In 2003, the Chinese population was infected with a virus causing Severe Acute Respiratory Syndrome (SARS) in Guangdong province. The virus was confirmed as a member of the Beta corona virus sub group and was named SARS-CoV. The infected patients exhibited pneumonia symptoms with a diffused alveolar injury which lead to acute respiratory distress syndrome (ARDS). SARS initially emerged in Guangdong, China and then spread rapidly around the globe with more than 8000 infected persons and 776 diseases. A decade later in 2012, a couple of Saudi Arabian nationals were diagnosed to be infected with another corona virus. The detected virus was confirmed as a member of corona viruses and named as the Middle East

Respiratory Syndrome Coronavirus (MERS-CoV). The World health organization reported that MERS corona virus infected more than 2428 individuals and 838 deaths. MERS-CoV is a member beta-coronavirus subgroup and phylogenetically diverse from other human-CoV. The infection of MERS CoV initiates from a mild upper respiratory injury while progression leads to severe respiratory disease. Similar to SARS coronavirus, patients infected with MERS-coronavirus suffer pneumonia, followed by ARDS and renal failure. Recently, by the end of 2019, WHO was informed by the Chinese government about several cases of pneumonia with unfamiliar etiology.

The outbreak was initiated from the seafood market in Wuhan city of China and rapidly infected more than 50 peoples. The live animals are frequently sold at the Hunan seafood market such as bats, frogs, snakes, birds, marmots and rabbits. On 12 January 2020, the National Health Commission of China released further details about the epidemic, suggested viral pneumonia. From the sequence-based analysis of isolates from the patients, the virus was identified as a novel coronavirus. Moreover, the genetic sequence was also provided for the diagnosis of viral infection. Initially, it was suggested that the patients infected with Wuhan coronavirus induced pneumonia in China may have visited the seafood market where live animals were sold or may have used infected animals or birds as a source of food. However, further investigations revealed that some individuals contracted the infection even with no record of visiting the seafood market. These observations indicated a human to the human spreading capability of this virus, which was subsequently reported in more than 100 countries in the world. The human to the human spreading of the virus occurs due to close contact with an infected person, exposed to coughing, sneezing, respiratory droplets or aerosols. These aerosols can penetrate the human body (lungs) via inhalation through the nose or mouth (Fig. 2).

Primary reservoirs and hosts of corona viruses:

The source of origination and transmission are important to be determined in order to develop preventive strategies to contain the infection. In the case of SARS-CoV, the researchers initially focused on raccoon dogs and palm civets as a key reservoir of infection. However, only the samples isolated from the civets at the food market showed positive results for viral RNA detection, suggesting that the civet palm might be secondary hosts. In 2001 the samples were isolated from the healthy persons of Hongkong and the molecular assessment showed 2.5% frequency rate of antibodies against SARS-coronavirus. These indications suggested that SARS-coronavirus may be circulating in humans before causing the outbreak in 2003. Later on, Rhinolophus bats were also found to have anti-SARS-CoV antibodies suggesting the bats as a source of viral replication. The Middle East respiratory syndrome (MERS) coronavirus first emerged in 2012 in Saudi Arabia. MERS-coronavirus also pertains to beta-coronavirus and having camels as a zoonotic source or primary host. In a recent study, MERS-coronavirus was also detected in Wuhan, proffering that bats are the key host and transmitting medium of the virus. Initially, a group of researchers suggested snakes be the possible host, however, after genomic similarity findings of novel coronavirus with SARS-like bat viruses supported the statement that not snakes but only bats could be the key reservoirs. Further analysis of homologous recombination revealed that receptor binding spike glycoprotein of novel coronavirus is developed from a SARS-CoV (CoVZXC21 or CoVZC45) and a yet unknown Beta-CoV.

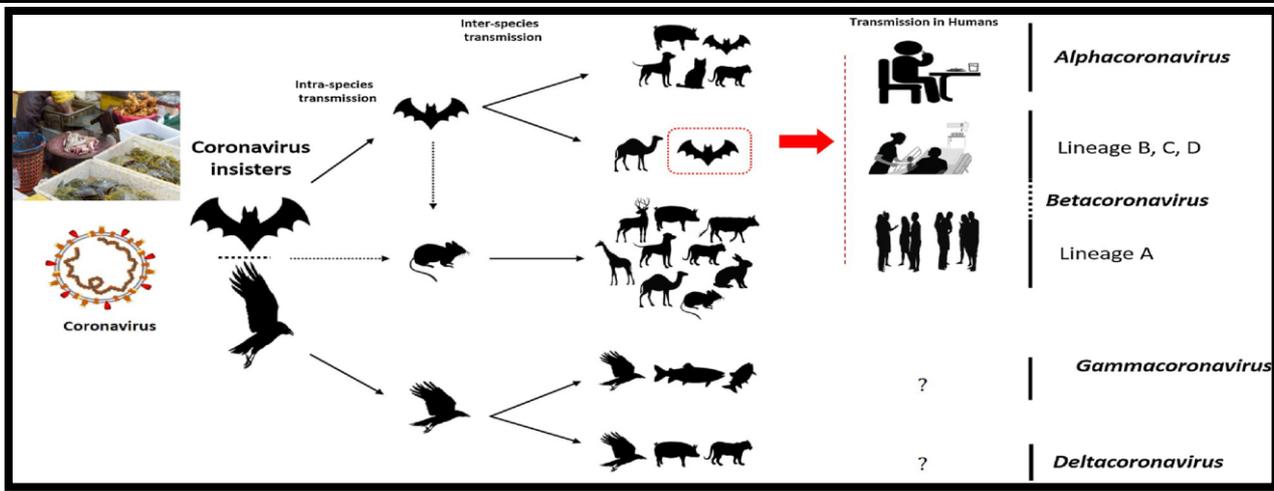


Fig. 2. s The key reservoirs and mode of transmission of corona virus (suspected reservoirs of SARS-CoV-2 are red encircled); only a and b corona viruses have the ability to infect humans, the consumption of infected animal as a source of food is the major cause of animal to human transmission of the virus and due to close contact with an infected person, the virus is further transmitted to healthy persons. Dotted black arrow shows the possibility of viral transfer from bat whereas the solid black arrow represents the confirmed transfer. [2]

Pathophysiology of COVID-19

Introduction:

Corona viruses are important human and animal pathogens. At the end of 2019, a novel corona virus was identified as the cause of a cluster of pneumonia cases in Wuhan, a city in the Hubei Province of China. It rapidly spread, resulting in an epidemic throughout China, followed by an increasing number of cases in other countries throughout the world. In February 2020, the World Health Organization designated the disease COVID-19, which stands for coronavirus disease 2019. The virus that causes COVID-19 is designated severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); previously, it was referred to as 2019-nCoV. This topic will discuss the epidemiology, clinical features, diagnosis, management, and prevention of COVID-19. Community-acquired corona viruses, severe acute respiratory syndrome (SARS) corona virus, and Middle East respiratory syndrome (MERS) corona virus are discussed separately.

EPIDEMIOLOGY

GEOGRAPHIC DISTRIBUTION

Since the first reports of cases from Wuhan, a city in the Hubei Province of China, at the end of 2019, more than 80,000 COVID-19 cases have been reported in China; these include all laboratory-confirmed cases as well as clinically diagnosed cases in the Hubei Province. A joint World Health Organization (WHO)-China fact-finding mission estimated that the epidemic in China peaked between late January and early February 2020. The majority of reports have been from Hubei and surrounding provinces, but numerous cases have been reported in other provinces and municipalities throughout China.

Increasing numbers of cases have also been reported in other countries across all continents except Antarctica, and the rate of new cases outside of China has outpaced the rate in China. These cases initially occurred mainly among travelers from China and those who have had contact with travelers from China. However, ongoing local transmission has driven smaller outbreaks in some locations outside of China, including South Korea, Italy, Iran, and Japan, and infections elsewhere have been identified in travelers from those countries. In the United States, several clusters of COVID-19 with local transmission have been identified throughout the country.

TRANSMISSION:

Understanding of the transmission risk is incomplete. Epidemiologic investigation in Wuhan at the beginning of the outbreak identified an initial association with a seafood market that sold live animals, where most patients had worked or visited and which was subsequently closed for disinfection. However, as the outbreak progressed, person-to-person spread became the main mode of transmission. Person-to-person spread of severe acute respiratory syndrome corona virus 2 (SARS-CoV-2) is thought to occur mainly via respiratory droplets resembling the spread of influenza. With droplet transmission, virus released in the respiratory secretions when a person with infection coughs, sneezes, or talks can infect another person if it makes direct contact with the mucous membranes; infection can also occur if a person touches an infected surface and then touches his or her eyes, nose, or mouth. Droplets typically do not travel more than six feet (about two meters) and do not linger in the air. However, given the current uncertainty regarding transmission mechanisms, airborne precautions are recommended routinely in some countries and in the setting of certain high-risk procedures in others. Viral RNA levels appear to be higher soon after symptom onset compared with later in the illness; this raises the possibility that transmission might be more likely in the earlier stage of infection, but additional data are needed to confirm this hypothesis. The reported rates of transmission from an individual with symptomatic infection vary by location and infection control interventions. According to a joint WHO-China report, the rate of secondary COVID-19 ranged from 1 to 5 percent among tens of thousands of close contacts of confirmed patients in China. In the United States, the symptomatic secondary attack rate was 0.45 percent among 445 close contacts of 10 confirmed patients. Transmission of SARS-CoV-2 from asymptomatic individuals (or individuals within the incubation period) has also been described. However, the extent to which this occurs remains unknown. Large-scale serologic screening may be able to provide a better sense of the scope of asymptomatic infections and inform epidemiologic analysis; several serologic tests for SARS CoV-2 are under development. SARS-CoV-2 RNA has been detected in blood and stool specimens. Live virus has been cultured from stool in some cases, but according to a joint WHO-China report, fecal-oral transmission did not appear to be a significant factor in the spread of infection.

Virology:

Full-genome sequencing and phylogenetic analysis indicated that the corona virus that causes COVID-19 is a beta corona virus in the same subgenus as the severe acute respiratory syndrome (SARS) virus (as well as several bat corona viruses), but in a different clade. The structure of the receptor-binding gene region is very similar to that of the SARS corona virus, and the virus has been shown to use the same receptor, the angiotensin-converting enzyme 2 (ACE2), for cell entry. The Corona virus Study Group of the International Committee on Taxonomy of Viruses has proposed that this virus be designated severe acute respiratory syndrome corona virus 2 (SARS-CoV-2). The Middle East respiratory syndrome (MERS) virus, another beta-corona virus, appears more distantly related. The closest RNA sequence similarity is to two bat corona viruses, and it appears likely that bats are the primary source; whether COVID-19 virus is transmitted directly from bats or through some other mechanism (eg, through an intermediate host) is unknown. In a phylogenetic analysis of 103 strains of SARS-CoV-2 from China, two different types of SARS-CoV-2 were identified, designated type L (accounting for 70 percent of the strains) and type S (accounting for 30 percent). The L type predominated during the early days of the epidemic in China, but accounted for a lower proportion of strains outside of Wuhan than in Wuhan. The clinical implications of these findings are uncertain.

Clinical Features

INCUBATION PERIOD:

The incubation period for COVID-19 is thought to be within 14 days following exposure, with most cases occurring approximately four to five days after exposure. In a study of 1099 patients with confirmed symptomatic COVID-19, the median incubation period was four days (inter quartile range two to seven days). Using data from 181 publicly reported, confirmed cases in China with identifiable exposure, one modeling study estimated that symptoms would develop in 2.5 percent of infected individuals within 2.2 days and in 97.5 percent of infected individuals within 11.5 days. The median incubation period in this study was 5.1 days.

SPECTRUM OF ILLNESS SEVERITY:

Most infections are not severe, although many patients with COVID-19 have critical illness. Specifically, in a report from the Chinese Center for Disease Control and Virology:

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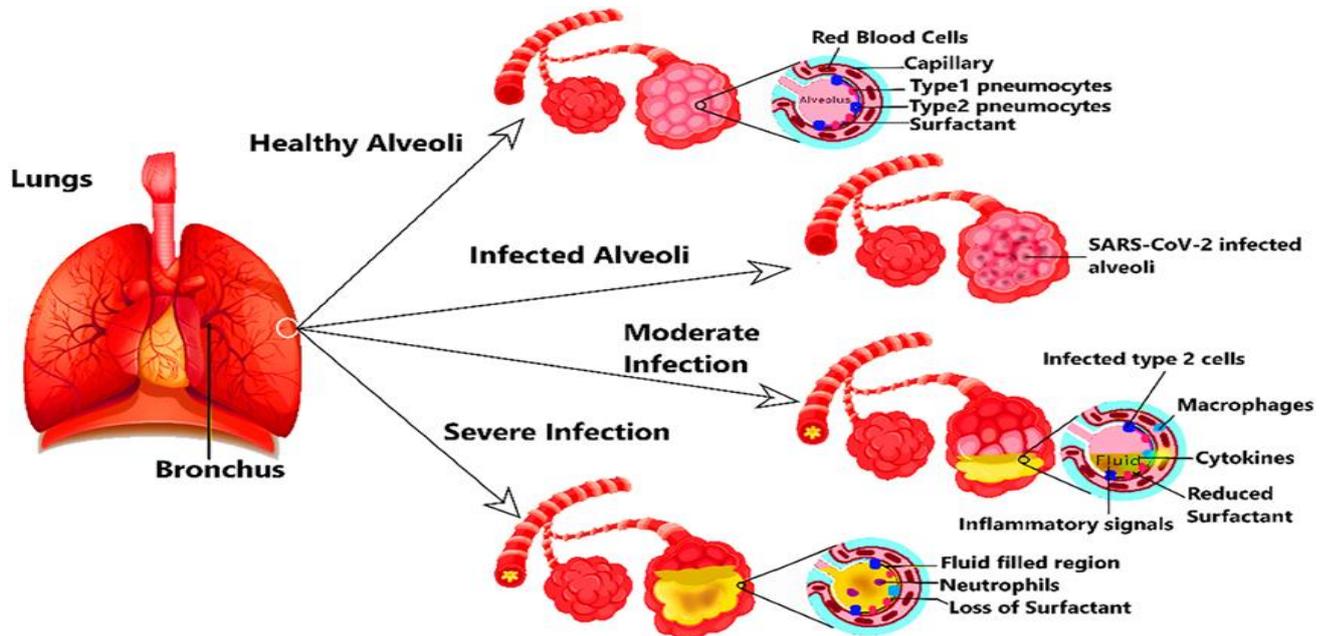
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ASYMPTOMATIC INFECTIONS:

Asymptomatic infections have also been described, but their frequency is unknown. In a COVID-19 outbreak on a cruise ship where nearly all passengers and staff were screened for SARS-CoV-2, approximately 17 percent of the population on board tested positive as of February 20; about half of the 619 confirmed COVID-19 cases were asymptomatic at the time of diagnosis. Even patients with asymptomatic infection may have objective clinical abnormalities. In another study of 24 patients with asymptomatic infection who all underwent chest computed tomography (CT), 50 percent had typical ground-glass opacities or patchy shadowing, and another 20 percent had atypical imaging abnormalities. Five patients developed low-grade fever, with or without other typical symptoms, a few days after diagnosis.

Symptoms reported after COVID-19 infection

Common symptoms include fatigue, shortness of breath and a decline in mental abilities like memory or brain fog (cognitive dysfunction). The case definition does not include an exhaustive list of reported symptoms. As studies continue, we can expect to learn more.



The most common symptoms are shown in the figure below.

Fig:3 Symptoms reported after COVID-19 infection

MECHANISM OF ENTRY AND REPLICATION OF SARS-COV-2 INSIDE THE HUMAN CELL:



Fig 4: Cycle/Stages of covid-19 infection in lungs

The virus enters the body through the nose, eyes, or mouth. The spike protein binds specifically to the ACE2 receptors present on the type 2 pneumocytes in the alveoli in the lungs, just like the SARS-CoV1. The type 2 pneumocytes produce surfactants that reduce the collapsing pressure and also decrease the surface tension in alveoli; the binding of the ACE2 receptor allows the entry of the virus into the host cell due to host cell proteases that cleave the spike protein of the virus.

The virus enters the host cell either by direct cell entry by membrane fusion or by endocytosis. Unlike a typical flu virus that travels to the nucleus once inside the host cell, the SARS-CoV-2 releases its positive-sense RNA into the host cell cytoplasm. This RNA is translated into polyproteins, pp1a and pp1ab. These help in the replication and transcription of the viral RNA. The replication of positive-sense RNA using RNA-dependent RNA polymerase enzyme gives a negative-sense RNA. The negative-sense RNA is either replicated to give positive-sense RNAs (incorporated in the viral genome) or transcribed. The transcribed mRNAs can be translated to produce viral proteins, like the spike, membrane, envelope, and nucleocapsid proteins. The host cell ER carries the proteins to the Golgi apparatus, where they are packaged into vesicles and assembled near the host cell membrane. The new viruses that are formed exit the host cell by exocytosis to infect other cells. This process results in death of the Host cell.

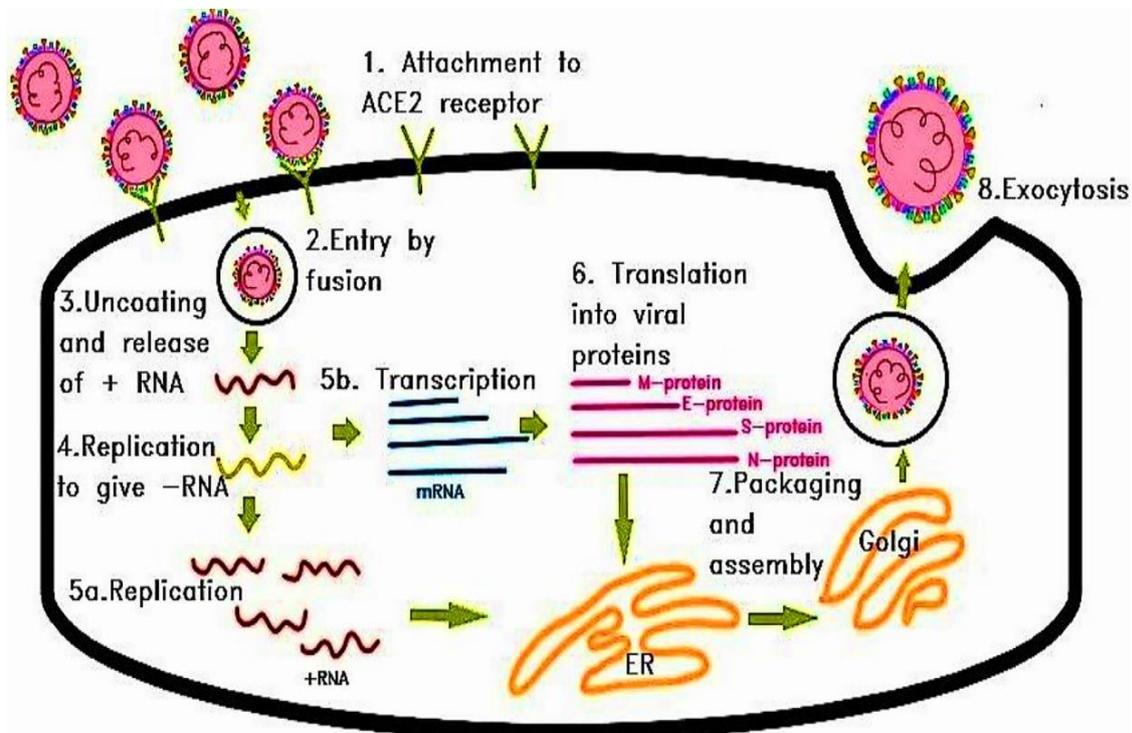


Fig No.05: Stages of replication of SARS-CoV-2

CLINICAL PRESENTATION:

Pneumonia appears to be the most frequent serious manifestation of infection, characterized primarily by fever, cough, dyspnea, and bilateral infiltrates on chest imaging. There are no specific clinical features that can yet reliably distinguish COVID-19 from other viral respiratory infections. In a study describing 138 patients with COVID-19 pneumonia in Wuhan, the most common clinical features at the onset of illness were

- Fever in 80 percent
- Fatigue in 70 percent

- Dry cough in 66 percent
- Sore Throat in 25 percent
- Diarrhea in 8 percent
- Dyspnea in 66 percent
- Anosmia 8 percent
- Sputum production in 30 percent

The dyspnea developed after a median of five days of illness. Acute respiratory distress syndrome developed in 20 percent, and mechanical ventilation was implemented in 12.3 percent. Other cohort studies of patients from Wuhan with confirmed COVID-19 have reported a similar range of clinical findings. However, fever might not be a universal finding. In one study, fever was reported in almost all patients, but approximately 20 percent had a very low grade fever $100.4^{\circ}\text{F}/38^{\circ}\text{C}$. In another study of 1099 patients from Wuhan and other areas in China, fever (defined as an auxiliary temperature over $99.5^{\circ}\text{F}/37.5^{\circ}\text{C}</math>) was present in only 44 percent on admission but was ultimately noted in 89 percent during the hospitalization. Other, less common symptoms have included headache, sore throat, and rhino rhea. In addition to respiratory symptoms, gastrointestinal symptoms (e.g., nausea and diarrhea) have also been reported in some patients, but these are relatively uncommon. According to the WHO, recovery time appears to be around two weeks for mild infections and three to six weeks for severe disease.$

LABORATORY FINDINGS:

The laboratory parameters revealed that 39 patients (61.9%) had hypo albuminemia , 27 patients (42%) had anemia, and 34 patients (53.9%) had lymphopenia [Table 1].

Table 1: Distribution of abnormal laboratory findings in COVID-19 patients

Abnormal findings	Frequency (%)
Anemia	27 (42.86)
Leucopenia	7 (11.11)
Lymphopenia	34 (53.97)
Thrombocytopenia	21 (33.33)
AKI	10 (15.87)
Hypoalbuminemia	39 (61.90)

AKI: Acute kidney injury

On chest X-ray, the most common pattern observed was bilateral infiltrates in 47.62% (30) whereas 31% (20) of the patients had normal chest X-rays.

LABORATORY TESTING :Patients who meet the criteria for suspect cases, as discussed above, should undergo testing for SARS-CoV-2 (the virus that causes COVID-19), in addition to testing for other respiratory pathogens, In the United States, the CDC recommends collection of specimens to test for SARS-CoV-2 from the upper respiratory tract (nasopharyngeal and or pharyngeal swab) and, if possible, the lower respiratory tract (sputum, tracheal aspirate, or broncho alveolar lavage). Induction of sputum is not indicated. Additional specimens (e.g., stool, urine) can also be collected. Respiratory specimen collection should be performed under airborne precautions.

Nucleic acid amplification tests (NAAT) for COVID-19 virus.

Routine confirmation of cases of COVID-19 is based on detection of unique sequences of virus RNA by NAAT such as real-time reverse-transcription polymerase chain reaction (rRT-PCR) with confirmation by nucleic acid sequencing when necessary. The viral genes targeted so far include the N, E, S and RdRP genes. Examples of protocols used may be found here. RNA extraction should be done in a bio safety cabinet in a BSL-2 or equivalent facility. Heat treatment of samples before RNA extraction is not recommended.

Laboratory confirmation of cases by NAAT in areas with no known COVID-19 virus circulation.

To consider a case as laboratory-confirmed by NAAT in an area with no COVID-19 virus circulation, one of the following conditions need to be met:

[1] A positive NAAT result for at least two different targets on the COVID-19 virus genome, of which at least one target is preferably specific for COVID-19 virus using a validated assay (as at present no other SARS-like corona viruses are circulating in the human population it can be debated whether it must be COVID-19 or SARS-like corona virus specific);

OR

[2] One positive NAAT result for the presence of betacoronavirus, and COVID-19 virus further identified by sequencing partial or whole genome of the virus as long as the sequence target is larger or different from the amp icon probed in the NAAT assay used.

Diagnosis

- Antiviral drugs. Researchers are testing the antiviral drugs favipiravir and merimepodib. Studies have found that the combination of lopinavir and ritonavir isn't effective.
- Anti-inflammatory therapy. Researchers study many anti-inflammatory drugs to treat or prevent dysfunction of several organs and lung injury from infection-associated inflammation.
- Dexamethasone. The corticosteroid dexamethasone is one type of anti-inflammatory drug that researchers are studying to treat or prevent organ dysfunction and lung injury from inflammation. Studies have found that this drug reduces the risk of death by about 30% for people on ventilators and by about 20% for people who need supplemental oxygen.

The U.S. National Institutes of Health has recommended dexamethasone for people hospitalized with COVID-19 who are on mechanical ventilators or need supplemental oxygen. If dexamethasone isn't available, other corticosteroids, such as prednisone, methyl prednisolone or hydrocortisone, may be used. Dexamethasone and other corticosteroids may be harmful if given for less severe COVID-19 infection.

In some cases, the drugs remdesivir, tocilizumab or baricitinib may be given with dexamethasone in hospitalized people who are on mechanical ventilators or need supplemental oxygen.

- Immune-based therapy. Researchers study immune-based therapies, including convalescent plasma, mesenchymal stem cells and monoclonal antibodies. Monoclonal antibodies are proteins created in a lab that can help the immune system fight off viruses.
- Monoclonal antibody medications include sotrovimab; bebtelovimab; a combination of bamlanivimab and etesevimab; and a combination of casirivimab and imdevimab. Some monoclonal antibodies, including bamlanivimab and etesevimab and casirivimab and imdevimab, aren't effective against COVID-19 caused by the omicron variant. However, sotrovimab and bebtelovimab can be used to treat COVID-19 caused by the omicron variant.

These drugs are used to treat mild to moderate COVID-19 in people who have a higher risk of developing serious illness due to COVID-19. Treatment involves a single infusion given by a needle in the arm (intravenously) in an outpatient setting. To be most effective, these medications need to be given soon after COVID-19 symptoms start and before hospitalization.

Researchers also study the use of a type of immune-based therapy called convalescent plasma. The FDA has authorized for emergency use convalescent plasma therapy to treat COVID-19. Convalescent plasma is blood donated by people who've recovered from COVID-19. Convalescent plasma with high antibodies may be used to treat some hospitalized people with COVID-19 who are either early in their illness or have weakened immune systems. TREATMENT OR RATIONAL USE OF DRUG FOR COVID-19:

Rational use of drugs can be defined as prescribing the right drug, in sufficient dose for the adequate duration and suitable to the clinical requirements of the patients at least cost.

Emergency use authorization (EUA) Emergency investigational new drug (EIND) give the permission to use the following drug on covid 19.

1. Remdesivir
2. Tocilizumab
3. Lopionavir&riritanovir
4. Chloroquine&hydroxychloroquine

1. Remdesivir

Remdesivir is investigational intravenous drug with broad spectrum activity.

Intravenous remdesivir is approved by the Food and Drug Administration (FDA) for the treatment of COVID-19 in adult and pediatric patients.

It is approved for the treatment of mild to moderate COVID-19 in high-risk, no hospitalized patients (i.e., a 3-day course initiated within 7 days of symptom onset) and for the treatment of hospitalized patients with COVID-19 (i.e., a 5-day course)

- Renal or hepatic dysfunction (EGFR<30 ml/min/m²; AST/ALT >5 times ULN (Not an absolute contradiction)
- Pregnancy or lactating females
- Children (< 12 years of age)
- Patients who are NOT on oxygen support or in home settings

- Dose: 200 mg IV on day 1 followed by 100 mg IV daily for 4 days (total 5 days)
- Side effects: severe headache, fast, slow, or pounding heartbeats, wheezing, trouble breathing, swelling in your face, nausea, fever, chills, or shivering, itching, sweating.

1. Tocilizumab

- Tocilizumab known as traditional Actemra and Atlizumab is an immunosuppressive humanized monoclonal antibody drug.
- This drug is mainly used for the treatment of rheumatoid arthritis (RA) and systemic juvenile idiopathic arthritis.
- Tocilizumab selectively and competitively binds to soluble expressing the IL-6 receptor (IL-6) and then blocking the signaling caused by IL-6. This drug displays dose-dependent, nonlinear pharmacokinetics and has a long elimination half-life.
- Presence of severe disease (preferably within 24 to 48 hours of onset of severe disease/ICU admission).

I. Recommended single dose: 4 to 6 mg/kg (400 mg in 60kg adult) in 100 ml NS over 1 hour.

- Storage condition: stored refrigerated at 2 to 8°C (36 to 46°F)

TABLE I. Side effects: common side effects:

Respiratory tract infections, headache, hypertension, elevation in liver test

Serious side effect:

Tuberculosis, sepsis, fungal infection

3. Chloroquine & Hydroxychloroquine

- Chloroquine is an anti-malarial drug that was developed in 1934. Hydroxychloroquine, an analogue of chloroquine, was developed in 1946. Hydroxychloroquine is used to treat autoimmune diseases, such as systemic and rheumatoid arthritis, in addition to malaria.
- Dose: Patients in the hydroxychloroquine arm received hydroxychloroquine 800 mg on Day 1 followed by 400 mg daily for an additional 6 days.
- Adverse Effects:
Chloroquine and hydroxychloroquine have similar toxicity profiles, although hydroxychloroquine is better tolerated and has a lower incidence of toxicity than chloroquine. Cardiac adverse events that have been reported in people who received hydroxychloroquine include QTc prolongation, Torsades de Pointes, ventricular arrhythmia, and cardiac deaths.

4. Lopinavir-ritonavir

- The Lopinavir-ritonavir combination is one of the repurposed drugs currently used in the treatment of COVID-19. They are protease inhibitors used for treating HIV infection. Both these drugs are suggested to inhibit SARS-CoV-2-like protease enzyme.
- LPV is a peptidomimetic HIV type 1 aspartame protease inhibitor that acts by binding to its catalytic site, thereby, preventing the cleavage of viral poly protein precursors into mature, functional proteins that are necessary for viral replication. LPV is usually given in combination with low booster doses

of ritonavir which improves the pharmacokinetics of LPV by slowing its hepatic metabolism through the inhibition of cytochrome P450 3A4 enzyme.

- Dose: lopinavir in adults is 800 mg daily in combination with 200 mg of ritonavir, usually in two divided doses.

Prevention:

In the health care setting:

Screening and precautions for fever or respiratory symptoms

- Screening patients for clinical manifestations consistent with COVID-19 (eg, fever, cough, dyspnea) prior to entry into a health care facility can help identify those who may warrant additional infection control precautions. This can be done over the phone before the patient actually presents to a facility. Any individual with these manifestations should be advised to wear a facemask. Separate waiting areas for patients with respiratory symptoms should be designated, if possible, at least six feet away from the regular waiting areas. Symptomatic patients should also be asked about recent travel or potential COVID-19 exposure in the prior 14 days to determine the need for evaluation for COVID-19. In some settings, such as long-term care facilities, the United States Centers for Disease Control and Prevention (CDC) recommends that standard, contact, and droplet precautions in addition to eye protection be used for any patient with an undiagnosed respiratory infection who is not under consideration for COVID-19. This may help reduce the risk of spread from unsuspected COVID-19 cases. Infection control precautions for suspect COVID-19 cases are discussed below. In locations where community transmission is ongoing, postponing elective procedures or non-urgent visits and using virtual (e.g., through video communication) visits may be useful strategies to reduce the risk of exposure.

Infection control for suspected or confirmed cases:

Infection control to limit transmission is an essential component of care in patients with suspected or documented COVID-19. In one report of 138 patients with COVID-19 in China, it was estimated that 43 percent acquired infection in the hospital setting. Individuals with suspected infection in the community should be advised to wear a medical mask to contain their respiratory secretions prior to seeking medical attention. In the health care setting, the World Health Organization (WHO) and CDC recommendations for infection control for suspected or confirmed infections differ slightly:

- The WHO recommends standard, contact, and droplet precautions (i.e., gown, gloves, and mask), with eye or face protection. The addition of airborne precautions (ie, respirator) is warranted during aerosol-generating procedures (as detailed below).
- The CDC recommends that patients with suspected or confirmed COVID-19 be placed in a single-occupancy room with a closed door and dedicated bathroom. The patient should wear a facemask if being transported out of the room (e.g., for studies that cannot be performed in the room). An airborne infection isolation room (ie, a single-patient negative pressure room) should be reserved for patients undergoing aerosol-generating procedures (as detailed below).

- Any personnel entering the room of a patient with suspected or confirmed COVID-19 should wear the appropriate personal protection equipment: gown, gloves, eye protection, and a respirator (eg, an N95 respirator). If supply of respirators is limited, the CDC acknowledges that facemasks are an acceptable alternative (in addition to contact precautions and eye protection), but respirators should be worn during aerosol-generating procedures.

Aerosol-generating procedures include tracheal intubation, noninvasive ventilation, tracheotomy, cardiopulmonary resuscitation, manual ventilation before intubation, and bronchoscope. Nasopharyngeal or oropharyngeal specimen collection is not considered an aerosol generating procedure. For health care workers who have had a potential exposure to COVID-19, the CDC has provided guidelines for work restriction and monitoring. The approach depends upon the duration of exposure, the patient's symptoms, whether the patient was wearing a facemask, the type of personal protective equipment used by the provider, and whether an aerosol-generating procedure was performed.

DISCONTINUATION OF PRECAUTIONS:

The decision to discontinue infection control precautions for patients with COVID-19 should be made on a case-by-case basis in consultation with experts in infection prevention and control and public health officials. Factors to inform this decision include resolution of clinical signs and symptoms and negative results of reverse-transcription polymerase chain reaction (RT-PCR) testing for severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) on two sequential paired nasopharyngeal and throat specimens (i.e., four specimens total, each handled separately), with each pair collected ≥ 24 hours apart. Positive RT-PCR tests for SARS-CoV-2 were reported in four laboratory-confirmed COVID-19 patients after they had clinically improved and tested negative on two consecutive tests. The clinical significance of this finding is uncertain; it is unknown whether these individuals continued to shed infectious virus.

Environmental disinfection:

To help reduce the spread of COVID-19 virus, environmental infection control procedures should also be implemented. In United States health care settings, the CDC states routine cleaning and disinfection procedures are appropriate for COVID-19 virus. Products approved by the Environmental Protection Agency (EPA) for emerging viral pathogens should be used; a list of EPA-registered products can be found here. Specific guidance on environmental measures, including those used in the home setting, is available on the CDC and WHO websites. Additional information is also found in a separate topic review. The importance of environmental disinfection was illustrated in a study from Singapore, in which viral RNA was detected on nearly all surfaces tested (handles, light switches, bed and handrails, interior doors and windows, toilet bowl, sink basin) in the airborne infection isolation room of a patient with symptomatic mild COVID-19 prior to routine cleaning. Viral RNA was not detected on similar surfaces in the rooms of two other symptomatic patients following routine cleaning (with sodium dichloroiso-cyanurate). Of note, viral RNA detection does not necessarily indicate the presence of infectious virus. It is unknown how long SARS-CoV-2 can persist on surfaces; other corona viruses have been tested and may survive on inanimate surfaces for up to six to nine days without disinfection. In a study evaluating the survival of viruses dried on a plastic surface at room temperature, a specimen containing SARS-CoV (a virus closely related to SARS-

CoV-2) had detectable infectivity at six but not nine days. However, in a systematic review of similar studies, various disinfectants (including ethanol at concentrations between 62 and 71 percent) inactivated a number of corona viruses related to SARS-CoV-2 within one minute.

Preventing exposure in the community—

The following general measures are recommended to reduce transmission of infection:

- Diligent hand washing, particularly after touching surfaces in public. Use of hand sanitizer that contains at least 60 percent alcohol is a reasonable alternative if the hands are not visibly dirty.
- Respiratory hygiene (e.g., covering the cough or sneeze).
- Avoiding touching the face (in particular eyes, nose, and mouth).
- Avoiding crowds (particularly in poorly ventilated spaces) if possible and avoiding close contact with ill individuals.
- Cleaning and disinfecting objects and surfaces that are frequently touched. The CDC has issued guidance on disinfection in the home setting. [3]

Co morbidity & COVID-19:

Coronavirus disease 2019 (COVID-19) is presented with asymptomatic, mild, or severe pneumonia-like symptoms. COVID-19 patients with diabetes, chronic obstructive pulmonary disease (COPD), cardiovascular diseases (CVD), hypertension, malignancies, HIV, and other comorbidities could develop a life-threatening situation. SARS-CoV-2 utilizes ACE-2 receptors found at the surface of the host cells to get inside the cell. Certain co morbidities are associated with a strong ACE-2 receptor expression and higher release of pro-protein converts that enhances the viral entry into the host cells. The co morbidities lead to the COVID-19 patient into a vicious infectious circle of life and are substantially associated with significant morbidity and mortality. The co morbid individuals must adopt the vigilant preventive measure and require scrupulous management. In this review, we rigorously focused on the impact of common morbidities in COVID-19 patients and recapitulated the management strategies with recent directions. We found limited resources describing the association of co morbidities in COVID-19; however, our review delineates the broader spectrum of co morbidities with COVID-19 patients.

Risks of COVID-19:

SARS-CoV-2 infects people of all age groups, but individuals aged above 60 years, along with co morbidities such as diabetes, chronic respiratory disease, and cardiovascular diseases, are at a higher risk of developing infection. The underlying mechanism of SARS-CoV-2 remains elusive; however, it is established that the virus utilizes ACE-2 receptors, which are found on the surface of the host cells to get inside the cell. High-plasmapro-inflammatory cytokines, lymphopenia, and atypical respiratory manifestations are the attributes of COVID-19 patients with high-grade fever and breathing problems.

Several metabolic and infectious diseases impact the severity of COVID-19 and play a pivotal role in establishing complex symptoms.

Diabetes and COVID-19:

People with diabetes are inclined to get infections due to impaired phagocyte cell capabilities. Further, several other factors increase the risk of COVID-19 in diabetic patients. An elevated level of ACE-2 receptors found to be causally related to diabetes by Mendel an randomization analysis; this might prejudice people with diabetes to SARS-CoV-2 infection. Furin is a type 1membrane-bound protease expressed in high levels in diabetic patients. This proproteinconvertase involved in the entry of the virus inside the host cell by decreasing the SARS-CoV-2dependency on human proteases. The SARS-CoV-2 spike (S) protein attach to the ACE-2 receptors is activated by then or levels. This pre-activation of S protein allows the viral entryinto the cell and escapes from the human immune system. Hence, a deregulated immune response with increased ACE-2receptors and farina expression may lead to a higher lung inflammation rate and lower insulin levels. The convenient entry of virus leads to a life-threatening situation for diabetic patients. Moreover, the impaired function of T-cell and elevated levels of interleukin-6 (IL-6) also plays a decisive role in developingCOVID-19 disease in diabetics. Emerging data about COVID-19suggests that 11–58% of all COVID-19 patients have diabetes, and an 8% COVID-19 fatality rate has been reported in diabetic patients. The risk for ICU admissions in COVID-19 individuals with diabetic co morbidity is 14.2% higher than individuals without diabetes.

Obesity and COVID-19:

Obesity (BMI ≥ 30 kg/m²) is linked with reduced oxygen saturation of blood by compromised ventilation at the base of the lungs. Additionally, some other characteristic features of low-grade inflammation due to obesity may occur, such as the abnormal secretions of cytokines, adipokines, and interferon consequences in compromised immune response. Surprisingly, obesity wasnot a risk factor for COVID-19 in the early reports from China, Italy, and the United States. Nevertheless, the high number of COVID-19 cases observed in the regions with moreobese people from Europe and North America. Thus, it isneeded to explore the relationship of obesity with the frequency of COVID-19. Obesity is one of the less highlighted co morbidities in COVID-19 infections. Though, 47.6% of obese people get infected with COVID-19 and out of these patients, 68.6% receive ventilation in a critical situation. Hence, a high body mass index (BMI) is a risk factor in COVID-19 severity, and obese peoples should take extra care to prevent themselves in this current pandemic.

COPD and COVID-19:

COVID-19illness can lead to the development of hypoxemia in15–20% of the patients, which require ventilator support in adverse conditions. The transition in the inflammatory response, microbiome imbalance, weak immunity, continual mucus production, use of respiratory corticosteroids, and structural damages are involved in establishing COPD. COPD and other chronic disorderswere also associated with SARS (1.4%) and MERS (13%) infections. Although earlier studies did not report a high number of COVID-19 cases with COPD, the expression of ACE-2 receptors is increased in this disease, contributing to the establishment of severe symptoms among COVID-19 individuals, including structural damage to lungs,

weak immunity and hyper mucous production. COP observed in 50–52.3% of the total ICU admitted COVID-19 cases, lead to high mortality among these patients with increased mucous production and blockage of air passages.

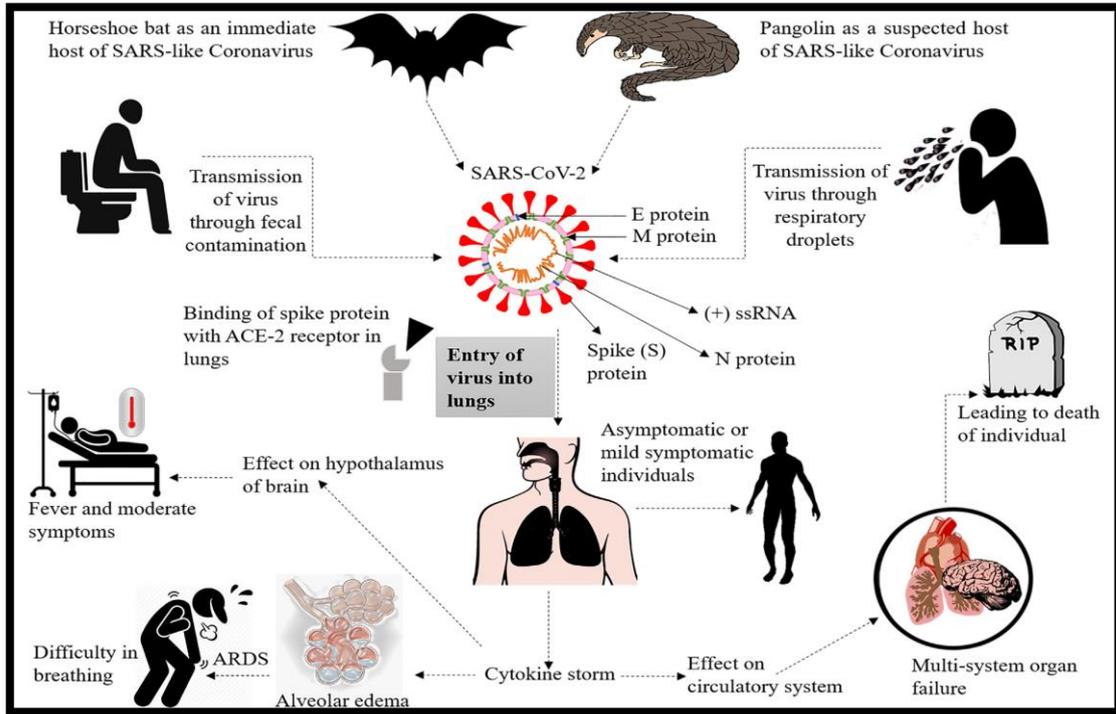


Fig.6: This figure depicts the pathogenesis of SARS-CoV-2 as it is transmitted from bat through pangolin as an intermediate host and transferred from human to human. The virus utilizes the ACE-2 receptor present in alveolar cells in the lungs, hepatocytes, and kidneys, and affects the host’s biochemistry by entering cells. SARS-CoV-2 causes acute respiratory distress syndrome (ARDS) by entering into the lungs and generating cytokine storms, which can affect the circulatory system that leads to morbidity and mortality.

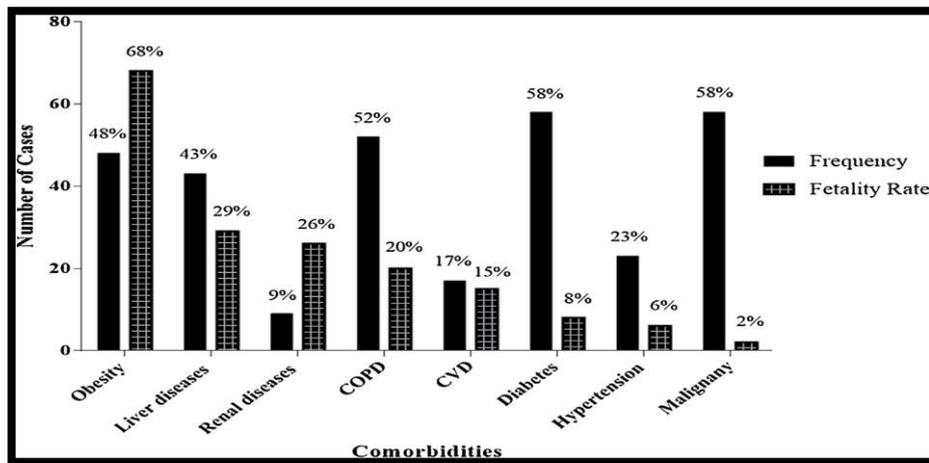


Fig. 7 .The frequency of co morbidity and its fatality in COVID-19 infections.

Asthma and COVID-19:

It is known for almost 18 years that asthmatic people are more prone to develop viral infections. If left uncontrolled, these viral infections can develop severe symptoms. People with asthma haven delayed innate antiviral immune response and impaired secretion of IFN- γ , which makes people more susceptible to develop severe complications. Asthma, along with other pulmonary chronic diseases, were associated with SARS (1.4%) and MERS (13%), which induced severe symptoms. Based on history, it is assumed that asthma could be among a potent risk factor of COVID-19. A comparative analysis of critical and non-

critical COVID-19 patients in Wuhan revealed no significant association of SARS-CoV-2 with asthma and other self-reported allergies, such as food allergy, atopic dermatitis, and allergic rhinitis. However, the risk of developing severe disease in COVID-19 patients is associated with asthmatic smokers, particularly geriatric individuals. Though asthma is not directly associated with COVID-19 infections, people with other complications and respiratory diseases are more likely to become entangled during asthma.

Hypertension and COVID-19:

Uncontrolled blood pressure is associated with COVID-19 infection and also with a high case fatality rate (CFR). In China, 23% of hypertensive COVID-19 cases were reported with 6% CFR, and the number continuously inclined due to pandemic anxiety. In patients suffering from hypertension, ACE-2 inhibitors, and angiotensin receptor blockers (ARBs) are frequently used for the treatment purpose. These inhibitors, when used in a high amount, up regulate expression of the ACE-2 receptor, thereby leading to increased susceptibility to SARS-CoV-2 infection. Higher expression of receptor cells on the lungs makes the infection more vulnerable, and chances of severe lung injury and increased chances of respiratory failure. On the other hand, experimental studies suggest ACE-2 is a potent anti-inflammatory agent and protects against lung injury, kidney injury, and respiratory distress syndrome, which are the common severe complications in COVID-19. The use of ACE inhibitors and ARBs enhance ACE 2, which reduces the inflammatory action of angiotensin II. It is not clear either the use of ACE inhibitors or ARB is harmful or beneficial, but it is recommended to use these molecules to maintain the normal blood pressure. The steps in controlling blood pressure should remain an essential consideration in COVID-19 patients to reduce disease burden.

CVD and COVID-19:

CVD had a strong relationship with SARS (8%) and MERS (30%). Similarly, the increased prevalence of CVD observed in COVID-19 patients, most notably among those with severe sign and symptoms. A study in Wuhan noted 6.8% CVD non-survivors from 191 COVID-19 patients, while another research observed that 17% of the COVID-19 non-survivors had CVD. Although the mechanism behind the association between CVD and COVID-19 is not precise, whether it is a direct or indirect relationship, most of these COVID-19 patients reported with the compromised immune system that is common in patients with CVDs. High-risk of COVID-19 in pre-existing CVD patients might be due to ACE-2 receptors' presence on cardiac muscle cells, suggesting the potential involvement of the cardiovascular system in SARS-CoV-2 infection. Patients with CVD have a higher risk of developing acute coronary syndrome in acute infections. This syndrome escalates the myocardial demand, which eventually led to myocardial injury or infarction. Moreover, an increased rate of inflammatory cytokines in COVID-19 cases mediate atherosclerosis, procoagulative, and hemodynamic instability leading to ischemia and thrombosis. Cardiovascular co morbidities are common among COVID-19 patients who need immediate care to reduce morbidity and mortality.

Table 2: Comorbidities, symptoms, and targets concerning SARS-CoV-2.

Sr. no	Disease	SARS-COV-2 targets	Symptoms
1	Hypertension	Up regulate ACE-2 expression	Increased blood pressure with pneumonia
2	COPD	Up regulate ACE-2 expression	Severe hypoxemia
3	CVD	Impaired immune system	Myocardial injury, heart attack
4	Liver diseases	ACE-2 expression in liver cells, i.e., cholangiocytes, endothelial cells hepatocytes, and Kupffer cells	Elevated serum amino transferase
5	Malignancy	Impaired immune system	Adult respiratory distress syndrome
6	Asthma	Delayed innate antiviral immune response and delayed secretion of IFN- γ	Chronic respiratory diseases along with pneumonia-like symptoms
7	Renal diseases	Increase secretion of enzymes, dipeptidyl peptidase-4 and angiotensin-converting enzyme (ACE-2)	Acute kidney injury[AKI]
8	HIV	Antiretroviral therapy (ART) with the impaired immune system and ACE-2 receptor in the lungs	Pneumonia like symptoms with jaundice
9	Obesity	The abnormal secretions of cytokines, adipokines, and interferons	Chronic low-grade inflammation of abdominal obesity with effect on bronchi and lung parenchyma
10	Diabetes	ACE-2 expression, impaired T-cell function and increased interleukin-6 (IL-6)	Pneumonia like symptoms

Liver diseases and COVID-19

Liver injuries and abnormal liver biochemistry were reported in SARS, MERS, and now in COVID-19 infections. It implies that there is a relationship between abnormal liver enzyme secretion and corona virus infection. ACE-2 receptors present on liver cells mediate the entry of SARS-CoV-2 inside the liver cells. A months COVID-19 cases, 43.4% found with the abnormal secretion of aspartame amino transferase (AST), almandine amino transferees (ALT), and lactic dehydrogenate (LDH). However, no patient observed with the characteristic in trahepatic cholestasis or hepatic failure. Another study reported that 39.1% of COVID-19 patients exhibit elevated ALT and AST levels, and 6% have increased bilirubin levels. Around 29% of the COVID-19 patients demonstrate liver injury and develop severe complications during later stages of infections. Besides abnormal liver function tests in COVID-19, elevated enzymes may also be released from cardiac and body muscles. The changes in blood chemistry usually return to normal with-out significant hepatic morbidity. The liver damage is presented as a temporarily raised level of ALT and AST without hepatic failure in most of the patients; however, this could be detrimental in severe cases of COVID-19. Psychological stress, systemic inflammatory response, drug toxicity, and preceding hepatic diseases could be the underlying mechanisms of liver damage in SARS-CoV-2 infection. Currently, it is not evident that the SARS-CoV-2 is associated with hepatic cellular damage or in trahepatic cholestasis pathophysiology.

Malignancy and COVID-19

Patients suffering from any malignancy are at a higher risk of developing COVID-19 infection due to the weak immune response. SARS-CoV-2 gets an efficient replication environment in these individuals' to initiate infection. It has been found that 58.3% of the COVID-19 patients in a study had lung carcinoma, and 41.7% of them were taking immunotherapy, chemotherapy, or radiotherapy. However, none of these patients required ICU care during the hospital stay. A total of 2% fatality rate observed among the COVID-19 cases that already had malignancies.

HIV and COVID-19

A strain of CoV OC43 was isolated from HIV positive patient in 2003, and COVs have a firm history in HIV patients. People suffering from HIV infection have a high risk of developing COVID-19 disease because of the compromised immune system. After the first report of HIV affected patient positive for SARS-CoV-2, it was presumed that HIV infection is vulnerable co morbidity with COVID-19 infection. However, no significant correlation observed between HIV positive individuals having COVID-19 infections. As the outbreak expands, few more cases of COVID-19 were reported in HIV patients; nevertheless, all patients had mild disease without ICU admissions. There is no correlation between HIV and COVID-19 was observed in Thailand, which is one of the most HIV affected areas. Formerly, it was also speculated that antiretroviral drugs have potent activity against SARS-CoV-2, which could be a reason behind fewer cases of SARS-CoV-2 in HIV patients.

Renal diseases and COVID-19:

SARS-CoV-2 affects the kidneys by direct cellular injury or sepsis, leading to a cytokine storm. Recently, in Guangzhou, China scientists successfully isolated SARS-CoV-2 from the urine sample of an infected patient, which suggests the kidneys are also a potential target for SARS-CoV-2. Acute kidney injury (AKI) observed in 3–9% of the COVID-19 cases while it was reported in SARS (5%) and MERS (15%) patients with a 60%–90% mortality rate. There are chances of mortalities in addition to the risk of AKI in COVID-19. Besides, the raised levels of blood urea nitrogen, studies suggest that 26.7% of patients develop hematuria, 34% albumin-urea, 63% proteinuria. Patients with renal diseases are more likely to suffer from COVID-19 infection due to an increase in ACE-2 expression.

Patient management and challenges:

Knowing that effective antiviral medications and SARS-CoV-2 vaccines are not yet available, treating a COVID-19 patient is a major challenge for health care staff. COVID-19 with comorbidities leads to a vicious circle, enormous morbidity, and higher mortality in affected patients. The exposure to SARS-CoV-2 in comorbid individuals such as suffering from diabetes (lung inflammation and higher ACE-2 expression), CVDs (impaired heart and immune functions), and COPD (mucous production and inflammatory response) is detrimental to lungs, heart, kidneys, and liver. The complication send up with a deleterious effect on the patient due to multiple organ failure, shock, acute respiratory distress syndrome, heart failure, arrhythmias, renal failure, and, eventually, mortality. World Health Organization (WHO) and the National Institute of Health (NIH) have issued recommendations based on clinical evidence and expert guidance for

optimal care of COVID-19 patients. Management strategies vary according to the signs and symptoms of COVID-19 patients, e.g., those with no visible symptoms but positive for COVID-19 should be isolated at home. Patients with mild symptoms (absence of pneumonia and hypoxia) should start intervention, and the decision of inpatient and outpatient settings vary on case to case. While patients with severe symptoms of COVID-19 (respiratory distress) require intensive care using a ventilator and other supportive management. Therefore, efficient management can be accomplished by following these guidelines to manage further transmission and reduced mortality. Although most COVID-19 patients develop mild disease, about 20% of patients need hospitalization, and 5–8% develop severe symptoms and need intensive care and ICU admission. Differences in ICU admission rates in different countries are based on clinical practice and ICU admission requirements in that area moreover; predisposing factors such as age and co morbidity often influence the ICU administration rates. Different countries have a variable proportion of patients admitted to ICU as China reported 7–26%, 5–12% in Italy, and the highest rate recorded in the United States, 81%. Accurate data related to the duration of ventilation is limited, but sustained mechanical ventilation for two weeks or more is required to make patients breathe normally. Underlying diseases, such as hypertension, CVD, diabetes, malignancy, COPD, and asthma, have been reported as risk factors for severe disease and also increased the mortality rate; therefore better management with special consideration must be given to these patients. Most of the COVID-19 patients die due to pre-existing co morbidity; therefore, accurate morbidity must be separated into two groups, and different guidelines should be designed for these patients. The treatment for underlying diseases while treating COVID-19 must continue without any interruption. A vigorous hand washing, social distancing, and personal hygiene ameliorate the prevention from the COVID-19. The individuals with comorbidities should conscientiously apply personal protective strategies. The use of the influenza vaccine reduces 43%–55% risk of pneumonia in diabetic patients and could be used to differentiate influenza and COVID-19 symptoms. Due to the compromised immunity in comorbid patients, it is advised as long as the patient is suffering from mild or moderate symptoms that can be controlled at home; these patients should stay in home isolation. [5]

Post COVID Complications:

The pandemic caused by the virus SARS-CoV-2 is certainly the biggest challenge to global health today. From the first appearance of the disease that it causes (COVID-19) to the present-day, according to Johns Hopkins University, 71,792,772 cases and 1,606,685 deaths have been recorded around the world and still noted. As the duration of the pandemic extends and the number of patients who have recovered increases, many authors have been asking what chronic alterations COVID-19 might cause in this population. Cases of patients with persistent symptoms like dyspnea, fatigue, coughing, chest pain, malign and arthralgia have been reported in the literature; even among patients whose acute phase of the disease was mild. Other symptoms that have been reported include depression, cognitive disorders, headache and palpitations. The frequency with which these symptoms persist has not yet been well established, but some studies have shown that it may be high among patients who have recovered from COVID-19. In study published in JAMA, 143 patients were followed up for an average of 60 days after discharge from hospital and only 18

(12.6%) of them reported absence of symptoms relating to COVID-19, while 32% had one or two symptoms and 55% had three or more Repercussions impacting on quality of life occurred in 44.1% of the patients. Halpin et al. followed up a cohort of 100 patients in the United Kingdom after their discharge, including 32 who had been treated in an intensive care unit (ICU). In the ICU group, 72% continued to have some degree of persistent fatigue, around 50 days after their discharge; in the group treated in wards, persistent fatigue was reported in 60.3% of the cases. The chronic complications that may persist after infection with SARS-CoV-2 mainly affect the respiratory, cardiovascular, renal and neurological systems. One of the first studies to explore chronic alterations to the respiratory system caused by COVID-19 was published in June 2020. A total of 57 patients were followed up. They underwent pulmonary function test, a six-minute walking test and chest computed tomography (CT) 30 days after their discharge from hospital. Homographic alterations were seen in 31 patients (54.3%). Abnormalities in pulmonary function tests were detected in 43 patients (75.4%). In comparison with non-severe cases, the patients presenting severe disease had higher incidence of impairment of diffusing capacity of the lungs for carbon monoxide (DLCO) (75.6% versus 42.5%; $P = 0.019$). Diminished DLCO, lower respiratory muscle strength and abnormalities on pulmonary imaging were detected in more than half of these COVID-19 patients who were in the initial stage of convalescence. These data were not completely corroborated by Lemur et al who published a prospective study on 103 COVID-19 patients, including 15 cases that were considered severe and were treated in an ICU. Their aim was to report on their patient's quality of life, state of dyspnea, pulmonary infunction and chest CT findings, three months after their discharge from hospital. They found that a quarter of their patients continued to present opacities on chest CT and diminished diffusion capacity. However, in their sample, this was not reflected in increased dyspnea or impaired pulmonary function. ICU admission was the criterion most associated with the presence of pathological CT findings. Cardiac alterations have also been targeted in studies. In a cohort study on 100 patients who had recovered from COVID-19, cardiac magnetic resonance imaging (MRI) was performed on average 71 days after the disease had been diagnosed. Cardiac alterations were found in 78 patients and active myocardial inflammation in 60 patients. This occurred independent of the patient's preexisting conditions, disease severity, general evolution of the acute disease or length of time since the original diagnosis. Nonetheless, the long-term evolution of such cases remains uncertain. It also used cardiac MRI but studied a very specific population. They recruited 26 university athletes who had COVID-19. None of them needed hospitalization. Twelve of them (26.9%) reported having had mild symptoms, while the others had been asymptomatic. None of them were found to present any ST/T wave alterations in electrocardiograms, and all of them had ventricular volumes and functions that were within the normal range, through trans thoracic echocardiograms and cardiac MRI. None of the athletes presented elevated serum levels of troponin. Four of them (15%) had cardiac MRI findings consistent with myocarditis. Thus, the study by Rajpaetal. showed that even among asymptomatic individuals who are physically fit, cardiac alterations may occur. However, the importance of these findings remains unknown. The neurological alteration that has been most reported after COVID-19 is persistence of olfactory dysfunction. Ottertail analyzed the sense of smell of 50 consecutive patients, at least three weeks after they had recovered from an acute condition. Among these patients, 94% reported that they had suddenly lost their sense of

smell during the course of the disease. At the time of undergoing an olfactory test after their recovery, 38% of the patients still presented a deficiency, while 61.7% of them had completely recovered their sense of smell. Other neurological alterations that have also been described still need to be studied further to better characterize them. These include alterations of cognition and memory and deregulation of sleep. Some psychiatric alterations have also been reported, such as mood changes involving depression or anxiety. Other consequences, albeit hypothetical, may also impact the post-COVID-19 population. A study published in the journal *Future Oncology* theorized a potential carcinogenic effect from infection with SARS-CoV-2, especially in the pulmonary tissue, which would possibly translate in the future into increased risk of cancer among these patients. What can be expected from these chronic alterations, and even how to treat them, remains to be determined. A group of researchers in Recife, Brazil, published an interesting article in which they discussed the potential use of nuclear medicine as a means of mapping the chronic alterations to the lungs, kidneys, heart and endothelium that are caused by SARS-CoV-2. The pandemic is not over yet. The real damage that it will leave behind will certainly be much greater than what was initially thought. But right now, we need to get ready to treat these patients who have survived COVID-19 and often come back needing treatment for chronic complaints.[6]

Vaccination Programme:

Vaccines are substances that are used to provide immunity by stimulating the production of antibodies. Immunization is a process by which a person is made to develop resistance towards infectious diseases by using a vaccine. Immunization programme is one of the key interventions for protection of children from life threatening conditions, which are preventable. By this cost effective intervention program, morbidity and mortality due to vaccine preventable diseases has been drastically reduced. Through this review article the authors are trying to trace out the evolution of the vaccination programmes and the present status of the programme in view of the various difficulties it faces in recent times, which can lead to outbreaks and re-emergence of already controlled vaccine preventable diseases.

HISTORY AND EVOLUTION OF VACCINATION

Vaccines:

A vaccine is defined as “a substance used to stimulate the production of antibodies and provide immunity against one or several diseases, prepared from the causative agent of a disease, its products, or a synthetic substitute, treated to act as an antigen without inducing the disease” (Oxford Dictionary). A vaccine helps the body’s immune system to recognize and fight pathogens like viruses or bacteria, which then keeps us safe from the diseases they cause. Vaccines protect against more than 25 debilitating or life-threatening diseases, including measles, polio, tetanus, diphtheria, meningitis, influenza, typhoid and cervical cancer and currently COVID-19.

Vaccination:

Vaccination is one of the most cost-effective ways to prevent infectious diseases. Vaccination, or immunization, work by stimulating the immune system which is the natural disease-fighting system of the body. The healthy immune system is able to recognize invading bacteria and viruses and produce antibodies

to destroy or disable them to ward off a disease. In addition to the initial immunization process, periodic repeat doses or “boosters” can improve the effectiveness of immunizations.

Vaccine efficacy and effectiveness:

Vaccine efficacy and effectiveness are measures that compare the rates of disease between vaccinated and unvaccinated people in a community. Efficacy is measured in controlled clinical trials, whereas effectiveness is measured once the vaccine is approved for use in the general population. From these measures it is possible to identify the proportion of vaccinated people one would expect to be protected by the vaccine. Vaccine efficacy is proportionate reduction in disease attack rate (AR) between the unvaccinated (ARU) and vaccinated (ARV) whereas vaccine effectiveness is expressed as a rate difference, with use of the odds ratio (OR) for developing infection in spite of vaccination. Vaccine effectiveness predicts how a vaccine reduces disease in a population. By this, the net balance of benefits and adverse effects of the program can also be assessed. Vaccine potency (i.e., vaccine efficacy) is proportional to vaccine effectiveness. Vaccine effectiveness can be affected by various reasons like maintaining cold chain, accessibility of health care, affordability of vaccine which indirectly reflects the vaccination status of the target population.

What is herd immunity?

Herd immunity is an important mechanism by which the larger community is protected (also called community immunity). When most of a population is immune to an infectious disease, this provides indirect protection or population immunity (also called herd immunity or herd protection) to those who are not immune to the disease. For example, if 80% of a population is immune to a virus, four out of every five people who encounter someone with the disease won't get sick (and won't spread the disease any further). In this way, the spread of infectious diseases is kept under control. Depending how contagious an infection is, usually 50% to 90% of population needs immunity before infection rates start to decline. But this percentage isn't a “magic threshold” that we need to cross especially for a novel virus. Both viral evolution and changes in how people interact with each other can bring this number up or down. Below any “herd immunity threshold,” immunity in the population (for example, from vaccination) can still have a positive effect. And above the threshold, infections can still occur. The higher the level of immunity, the larger the benefit. This is why it is important to get as many people as possible vaccinated.

Vaccine potency and cold chain system:

All the vaccines are sensitive biological products. Some of the vaccines are sensitive to freezing, while some are sensitive to heat and others to light. Vaccine potency is ability of the vaccine to adequately protect the vaccinated persons. Vaccine potency can diminish when the vaccine is exposed to inappropriate temperatures and once lost, vaccine potency cannot be regained. So in order to maintain the quality, vaccines must be protected from temperature extremes. Vaccine quality and potency is maintained by using a process known as ‘cold chain’ that meets specific temperature requirements of the vaccines which ranges from 2-8 degree Celsius at the end user level. The ‘cold chain’ is a system of storing and transporting vaccines at recommended temperatures from the point of manufacture to the point of use. The role of the cold chain is to maintain the potency of vaccines in order to produce an adequate immune response in the

recipient. There is also a concept called 'reverse cold chain', which is a system of storing and transporting samples at recommended temperatures from the point of collection to the laboratory in order to test the potency of the vaccine.[7]

Vaccination in India:

Free vaccination against COVID-19 commenced in India on January 16, 2021, and the government is urging all of its citizens to be immunized, in what is expected to be the largest vaccination program in the world. Out of the eight COVID-19 vaccines that are currently under various stages of clinical trials in India, four were developed in the country. India's drug regulator has approved restricted emergency use of Covishield (the name employed in India for the Oxford-AstraZeneca vaccine) and Covaxin, the home-grown vaccine produced by Bharat Biotech.

Covishield by the Serum Institute of India

- Serum Institute of India (SII), Pane, has signed agreements with a few manufacturers such as Oxford-AstraZeneca, Codagenix, and Novavax. It is now producing at a large scale, the Oxford-AstraZeneca Adenovirus vector-based vaccine AZD1222 (which goes under the name "Covishield" in India). Covishield is produced under the "at-risk manufacturing and stockpiling license" from the Drugs Controller General of India (DCGI), and the Indian Council for Medical Research (ICMR). The ICMR funded the clinical trials of the Covishield vaccine developed with the master stock from Oxford-AstraZeneca.
- Ingredients :
 - L-Histidine
 - L-Histidine hydrochloride monohydrate
 - Magnesium chloride hexahydrate
 - Polysorbate 80
- Ingredients: COVAXIN® includes the following ingredients: COVAXIN® contains 6µg of whole-virion inactivated SARS-CoV-2 antigen (Strain: NIV-2020-770), and the other inactive ingredients such as aluminum hydroxide gel (250 µg), TLR 7 /8 agonist (imidazoquinolinone) 15 µg, 2-phenoxyethanol 2.5 mg, and phosphate buffer saline up to 0.5 ml. The vaccine (COVAXIN®) thus has been developed by using inactivated/ killed virus along with the above mentioned chemicals.
- Risk factor:
 - Headache
 - Fever
 - Malaise / bodyache
 - Nausea
 - Vomiting
 - Rashes

ZyCoV-D by Cadila Healthcare (ZyduCadila)

Production of another domestic COVID-19 vaccine, ZyCoV-D by Cadila Healthcare, Ahmadabad, based on the new plasmid DNA vaccine technology, is supported by the Department of Biotechnology, Government of India. Vaccines based on plasmid DNA technology are not licensed for public use. Plasmids are used as vectors to directly deliver the DNA encoding the target antigens into the body of the recipient. Sequence encoding for the pathogen's antigen is engineered into recombinant plasmid DNA. It is used as the vaccine vector so that the vaccine antigens are directly produced by human cells, thus eliciting an immune response. The Phase-I trials of this vaccine began on July 13, 2020, on volunteers of 18–55 years of age. As ZyCoV-D showed promise in a Phase-I study, and the drugmaker Cadila is currently finishing Phase-II trials on over 1000 volunteers across nine sites. This vaccine is administered intradermally.

Sputnik V by Dr. Reddy's Laboratories

- Gam-COVID-Vac, trade-named Sputnik V, is a COVID-19 vaccine developed by the Gamaleya National Center of Epidemiology and Microbiology of Moscow, Russia. Sputnik V is a two-vector viral vaccine based on human adenoviruses. Sputnik V uses adenoviruses Ad5 and Ad26. The recombinant adenovirus types 26 and 5 are biotechnology-derived and contain the SARS-CoV-2 S protein cDNA. Both of them are administered into the deltoid muscle. The Ad26-based vaccine is used on the first day and the Ad5 vaccine is used on the 21st day to boost immune responses. Russia's Sputnik V vaccine stipulates storage at a temperature not higher than -18°C . Dr. Reddy's Laboratories, located in Hyderabad, have received regulatory approval from the DCGI to conduct mid-to-late-stage human trials for Russia's Sputnik V vaccine in India. Russia's RDIF-Gamaleya Institute has signed agreements with more than one Indian company for the large-scale manufacture of their Sputnik V vaccine.
- Active substance: recombinant serotype 26 adenoviral particles containing the SARS-CoV-2 S protein gene, in the amount of $(1.0 \pm 0.5) \times 10^{11}$ particles per dose.
- Gam-COVID-Vac Combined vector vaccine (Component I) - 0.5 ml/dose & (Component II) - 0.5 ml/dose
- Component I - Gam-COVID-Vac Combined vector vaccine (Recombinant adenovirus serotype 26 particles containing the SARS-CoV-2 protein S gene, in an amount of $(1.0 \pm 0.5) \times 10^{11}$ particles / dose) to prevent SARS-CoV-2-induced coronavirus infection.
- Component II - Gam-COVID-Vac Combined vector vaccine (Recombinant adenovirus serotype 5 particles containing the SARS-CoV-2 protein S gene, in an amount of $(1.0 \pm 0.5) \times 10^{11}$ particles / dose) to prevent SARS-CoV-2-induced coronavirus infection.
- Adverse Events (AE)

In the study, 26,405 cases of AE have been reported to date, developed in 12,080 volunteers (35.8%). The AE reported in association with vaccination were observed in 9,323 volunteers (36.8%). Of which the commonly reported ($>3\%$) were flu like illness (20.1%), injection site reaction (19.1%), headache (4.1%), increased body temperature (3.8%) and asthenia (3.2%).

The AE reported in association with vaccination were observed in 677 volunteers of age >60 years of age (30.2%). Of which the commonly reported (>3%) were injection site reaction (12.7%), flu like illness (12.1%), headache (3.5%) and asthenia (3.4%).

mRNA vaccine (still unnamed) by Gennova Biopharmaceuticals Ltd:

The latest COVID-19 vaccine candidate that was granted conditional permission for Phases 1 and 2 of the human clinical trials by DCGI is the mRNA vaccine developed by the Pune-based Gennova Biopharmaceuticals Ltd in collaboration with HDT Biotech Corporation, USA.[8]

Conclusion:

The corona virus (COVID-19) spreads at an alarming rate all over the world. Pandemics propose an immense challenge to public health, health care systems, and global economic security. Special focus should be placed on understanding their pathophysiology to help better tailor and generate effective drug therapies and vaccinations. COVID-19 has challenged our existing knowledge, laws, and regulations and forced us to take measures as far as complete lockdown in various parts of the world. The high death toll of COVID-19 has stressed the need for prompt research and dissemination of updated information. This review summarized the pathophysiology of COVID-19 diagnosis tools and therapeutic options it also discussed the prevention and control measures considering an apparently upcoming wave of infection.

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